General Research

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Process Intensification Strategies and Sustainability Analysis for Amidation Processing in the Pharmaceutical Industry

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Abstract:

The amidation reaction between 4-chlorobenzoyl chloride (CBC) and diisopropylamine (DIPA) has been successfully intensified with the implementation of a number of Process Intensification (PI) options proven feasible in lab-scale experiments. Three PI options are explored – an intensified batch case, a continuous reaction case and a continuous whole-process case – and these are each compared to the batch base case. The PI options included reducing the amount of DIPA and solvents used in washes and carrying out continuous flow reaction in static mixers. A systematic series of washes and phase separation were also performed in a centrifugal extractor, which enabled a continuous extraction process to be developed. Promising experimental results were obtained using a Wiped Film Evaporator (WFE) for continuous solvent removal. Plant designs were generated for the options at a hypothetical throughput of 3.3 tonnes per year. Overall, the highest cost savings of up to 40% are estimated for the intensified batch case. In this particular process assumed to operate at 100% amide yield, the intensified batch is more suitable than continuous mode because the continuous options require a different mode of reagent addition resulting in a larger amount of water used to dissolve DIPA. However, if amide yield of 100% proves to be difficult to achieve in the

intensified batch, the continuous reaction process scheme may become a more desirable option, as demonstrated by a sensitivity analysis.

Keywords: Sustainability; amidation; continuous process; process intensification; pharmaceutical processing; static mixers

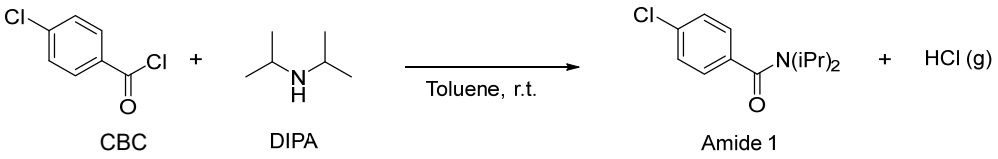
1. Introduction

Amide bond formation is one of the most common transformations in the pharma industry as amide bonds are often part of active pharmaceutical ingredients (APIs).[1] The most common practice is to perform direct amidation through the acylation of an amine with commercially available acid chloride on a large scale, as this approach avoids the need for acid activation.[2-5]

Direct amidation using commercially purchased 4-chlorobenzoyl chloride with diisopropylamine[6] is chosen as an example for this case study. One reason for selecting this reaction is because the product, 4-chloro-N,N-diisopropylbenzamide (amide 1), is a potential building block for the synthesis of many natural molecules.[7-9] Moreover, as this reaction demonstrates sufficiently complex process behaviours, it is considered a suitably challenging candidate for intensification. For example, the reaction involves multiple phases consisting of sticky gel-like solids and is moderately fast and exothermic. The separation and purification processes also present a realistic representation of a large number of processes commonly seen in pharmaceutical processing that involve extraction, handling of sticky solids and drying.

According to Faigl, et al. [6], the overall stoichiometry of amidation between 4-chloro benzoyl chloride (CBC) and diisopropylamine (DIPA) is given by Eq. (1) below. This reaction has no side product formation according to GC analysis.

Synthesis of amide 1 via amidation reaction between CBC and DIPA:



CBC DIPA Amide 1 (1)

Amide 1 is obtained from the reaction between CBC and DIPA in the presence of triethylamine (TEA) at ambient temperature. During the reaction, stoichiometric amounts of amine salts, given in Eq. (2) and (3), are formed while the HCl released is 'captured' by the amine bases. The amine salts are insoluble in toluene and present as solids.

By-product HCl neutralised by TEA to form amine salts:

$$Et_3N + HCl\,(g) \xrightarrow[\text{Toluene}]{} Et_3N.HCl\,(s) \quad (2)$$

By-product HCl neutralised by DIPA to form amine salts:

$$DIPA + HCl\,(g) \xrightarrow[\text{Toluene}]{} DIPA.HCl\,(s) \quad (3)$$

The objective of this work is to evaluate the sustainability benefits of the intensification of a conventional batch amidation process. In this study, the sustainability performance of this process chemistry under various whole-process intensification scenarios is assessed and compared at a hypothetical design scale of 3,3 tonnes per year. The benefits that could potentially be achieved are minimization of solvents, reagents and wastes, and better process safety. The approach, as highlighted in Figure 1, is based on a practical methodology developed by Teoh, et al. [10], applied to assess the feasibility of intensification of a batch process, by facilitating decision making at the early evaluation stage.

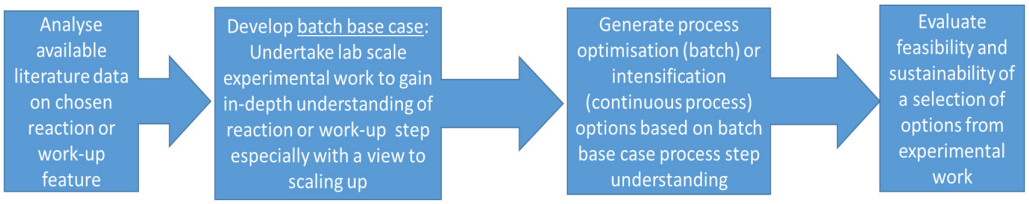


Figure 1. Methodology for developing process intensification options

2. Material and methods

2.1 Batch base case experiment/RC1 Experiment in Toluene Solvent System

Calorimetry was carried out using a Mettler Toledo RC1 in a 500 mL volume baffled reactor (6 cm i.d., AP01-0.5-RTC), glass 4-pitch blade turbine agitator (4 cm i.d.), RD10 control box and RC1 software. The RC1 reactor was charged with 233 g of toluene, 27 g of triethylamine (TEA) (1 M in toluene) and 30 g of diisopropylamine (DIPA) (1.1 M in toluene). The temperature of the reaction mixture was stabilized at 25 ˚C and was stirred at 450 rpm for 5 minutes before calibration and determination of the initial reaction mixture heat capacity. 32 g of CBC (0.5 M) was charged into the reactor over 15 minutes using a New Era 1000 syringe pump. 1 mL GC samples were drawn via a syringe every 30 min for conversion measurement. Full conversion was observed after 2 h of reaction time and the heat capacity of the final reaction mixture was calibrated. A large excess of 1 M HCl solution was added to quench the reaction by reacting with the excess DIPA.

2.2 Intensified Batch Case Experiment in Toluene-Water Solvent System

The main differences between the batch base case procedure and the intensified batch case in the reaction step were (i) the solvent system was changed to a biphasic toluene-water solvent mixture (ii) a higher CBC concentration was employed (iii) only one amine (DIPA) was used at a reduced mole eqv. than the combined amines. The rationale for these decisions will be discussed in section 3.2 below. The 150 mL baffled stirred tank reactor (4 cm i.d.) was

charged with 40 g of toluene and 10 g of DIPA (2.1 M in toluene), followed by 7 g of water. The liquid-liquid mixture was stirred at 400 rpm using a 4 blade pitched stainless steel agitator (2 cm i.d.) for 5 min. The jacket temperature was set at 20 °C. The stop watch was started once 8.5 g of CBC (1 M in toluene) was added dropwise manually via a syringe and the addition took less than a minute. The reaction was quenched after 5 min, upon addition of excess 1 M HCl solution under vigorous agitation. Samples from the organic phase were taken for GC analysis to quantify the reaction conversion.

2.3 Continuous Reaction in Static Mixer

In the setup shown in Figure 2, two peristaltic pumps (Watson Marlow 520S/R peristaltic pumps) were used to deliver toluene solution of CBC (1 M) and aqueous solution of DIPA (1.1 M) respectively. The two tubes carrying the two streams of solutions were connected in a head-on manner to a Tee-joint (CTA-2-STEL, 1/8 in, Hylok) and the combined outlet was connected to three Noritake static mixers (T3-17R-S) in series with a combined length of about 1 m, followed by a 24.5 m long bare 1/8 in i.d. PTFE tubing to provide a residence time of 5 min. Each static mixer was 10 cm in length and 3.4 mm in diameter and equipped with 17 rod-like elements positioned perpendicular to the flow direction of liquid. The peristaltic pumps were calibrated prior to the experiment. The static mixer setup was flushed with toluene and dried prior to each experiment by pushing compressed air through.

2 L of CBC in toluene (1 M) and 6 L of aqueous solution of DIPA (1.1 M) were prepared. The flow rate of the CBC stream into the reactor was set at 32.3 mL/min, while the flow rate of DIPA stream was set at 67.7 mL/min giving a total combined flowrate of 100 mL/min. Flow through the two pumps was started simultaneously and a combined flow rate of 100 mL/min was collected at the reactor outlet. Where necessary, adjustments in the individual

flowrates and concentrations of the CBC and DIPA streams in toluene and water respectively for the desired concentrations and flowrates. The reaction mixture was collected in two 5 L Schott bottle prefilled with 1 L of 2 M HCl solutions. The reaction mixture was mixed vigorously with the quench solution using a magnetic stirrer. The experiment was conducted for about 40 min with product in the first 10 min discarded to minimize collection during unsteady-state. The samples were taken from the organic phase at different time intervals and sent for GC analysis to quantify the reaction conversion.

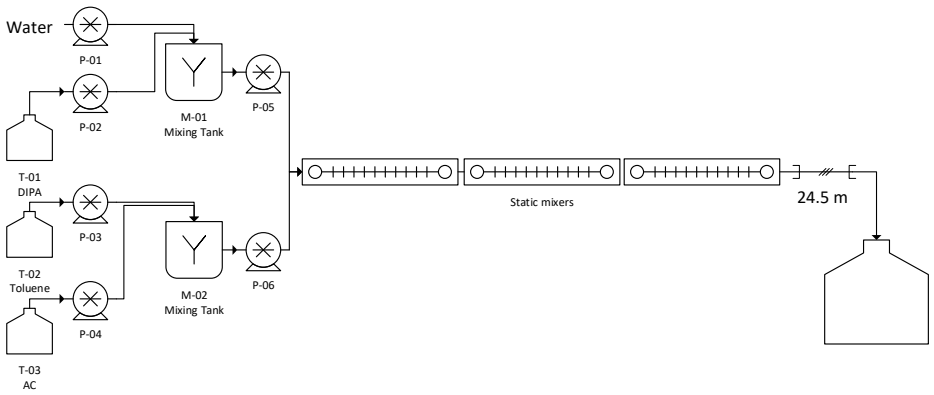


Figure 2. Schematic of the continuous static mixer setup

2.4 Continuous Extraction using Centrifugal Extractor

A schematic of a centrifugal extractor (CE) (CINC, V02) is shown in Figure 3. A weir size of 2.1 cm was used to separate toluene/water mixture under a rotational speed of 4000 rpm. All experiments were carried out in a single stage CINC V02. The experiment was initiated by switching on the agitator at 4000 rpm and pumping the heavy phase (aqueous) first, followed by the lighter phase (organic). After reaching steady state at the outlet flows, the experiment went on for several minutes. The CE was tested under three different operating conditions:

1) Separation of reaction mixture from the output of static mixer. The outlet of the static mixer setup flowed directly into the CE at 100 mL/min and the respective

phases were collected at separate outlets. The rate of collection of the organic phase was at about 30 mL/min, while the collection rate of the aqueous phase was 70 mL/min and clear phase separation was obtained.

2) Extraction of excess DIPA from organic phase using HCl solution. The organic phase from previous extraction and 1 M HCl solution were both pumped (Watson Marlow 520S/R peristaltic pumps) into the CE at 30 mL/min each via two separate inlets. The collection rates of both organic and aqueous phases were observed to be 30 mL/min each. Samples for analysis were taken from the organic phase for the detection of DIPA by qualitative NMR analysis.

3) Extraction of amine salt (if any) from organic phase using 1 M NaCl solution. Given there was no suitable analytical method to quantify amine salt in organic solvent, the quantity of NaCl solution used was referenced from the literature [6]. The organic phase from previous extraction and 1 M NaCl were pumped into the CE at 30 mL/min and 15 mL/min respectively. This was assumed to be effective in removing all the amine salt from the organic phase.

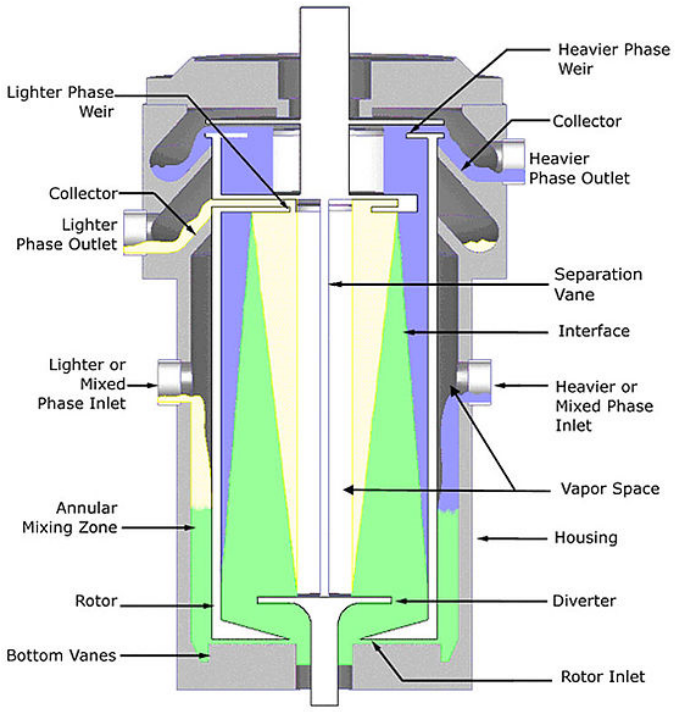


Figure 3. Schematic of CINC V02 centrifugal extractor (Courtesy of Vornfeld [11])

2.5 Wiped Film Evaporator

The wiped film evaporator (WFE) from Pope Scientific Inc., USA was used in continuous solvent evaporation as seen in Figure 4. The temperature of the still jacket was set at 70°C with a pressure of 0.09 bar and agitator speed of 250 rpm. The organic feed, obtained from the multiple CE washes, was admitted into the still at two different flow rates – 43 and 100 mL/min using a Watson Marlow 520S/R peristaltic pump. The total area of the heated area of the still was 0.108 m^2. The feed flowed down the evaporative surface, where the more volatile toluene vaporized, while the less volatile amide 1 concentrate continued flowing down the cylinder into the concentrate collector. The toluene was collected in the distillate receiver after passing through the condenser.

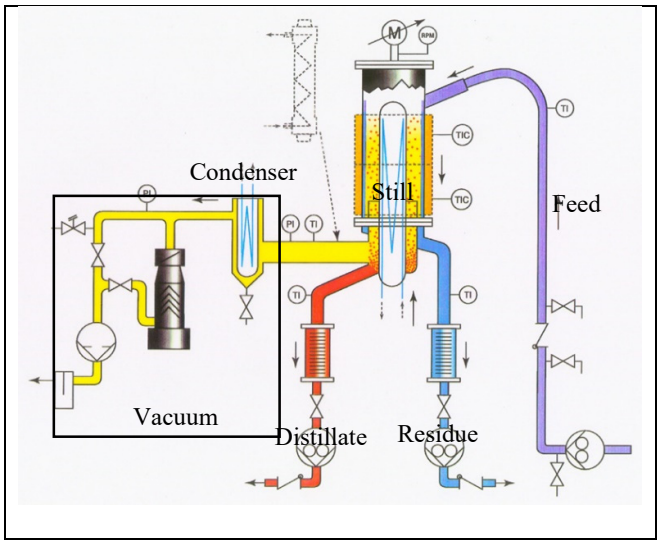


Figure 4. Schematic of POPE Wiped Film Evaporator (Courtesy of Pope Scientific Ltd[12])

2.6 Analytical Methods

2.6.1. Amide yield by GC analysis

Amide yield was determined by Gas Chromatography (GC) (Agilent Technologies 6890N GC system with 7693 autosampler and a HP-5 column) using the internal standard method. About 1 mL of reaction mixture was weighed and 1 mL of quench water was added, followed by 50 mg of internal standard (n-hexadecane) and mixed well. 20 µL of the organic layer was drawn and diluted in 1 mL of ethyl acetate before 1 µl of the mixture was injected into the column. Temperature was ramped from 150 to 210°C at 25°C/min over a run time of 15 min. The detector temperature was set at 280°C and the column was operated under a constant pressure of 11.02 psi.

2.6.2. Determination of DIPA.HCl salt concentration

To determine the DIPA.HCl formed during the amidation reaction, a minimum volume of water (0.28 L/mol CBC) was added to the reaction mixture slurry to dissolve the DIPA.HCl, followed by phase separation to obtain the mass of the aqueous layer. Assuming 100 % conversion and all the HCl formed is converted to DIPA.HCl and dissolved in the aqueous

layer, the aqueous DIPA.HCl concentration is expected to be about 490 g/L. A conductivity meter (Yokogawa FLXA21 Two-wire analyzer, with SC42-EP15 epoxy probe) was calibrated using different concentration of DIPA.HCl solutions. A 20-fold dilution of the aqueous layer with water brought the concentration to within the detection range for the conductivity meter (about 5-40 g/L).

3 Result and Discussions

3.1 Lab-scale batch experiments

Information regarding the basic physical behaviour of the reaction mixture (e.g. evolution of gas, formation of solids, phase behavior or interaction etc.) is often unavailable in the literature procedure and experiments need to be performed to bridge the gap. Table S1 lists the characteristics and observations of the amidation process obtained from preliminary lab-scale batch experiments. The batch process was evaluated step by step based on the processing functions. As highlighted by Teoh, et al. [10], the identification of suitable equipment and PI options will depend on the process engineers' experience and access to knowledge of the capabilities/characteristics of the relevant equipment. In this study, several possible PI options were proposed in Table S1 for further evaluation and validation. Note that PI options here refer to both process optimization and intensification strategies, where optimization relates to, for example, addition sequence of reagents or reducing the amount of wash water or HCl while intensification focuses primarily on continuous processing in reaction or purification steps. Ultimately, the optimization and intensification strategies are to be combined to achieve maximum sustainability benefits in the context of the amidation process under investigation here.

3.2 Generation of PI options

Based on the process information in Table S1, the key process issues where there is value to be gained (e.g. low yield, loss of product, generate waste, etc.) could be identified and the corresponding PI options that can potentially address the issues could be generated (Figure 5). The following are a list of promising PI options that presented strong cases to carry out experiments due to the potential benefits gained in product quality, efficiency, cost and safety.

1) Reduce the number and amount of reagents used
2) Reduce toluene usage
3) Reduce the wash mediums in workup
4) Continuous reaction
5) Continuous whole process (reaction and workup)

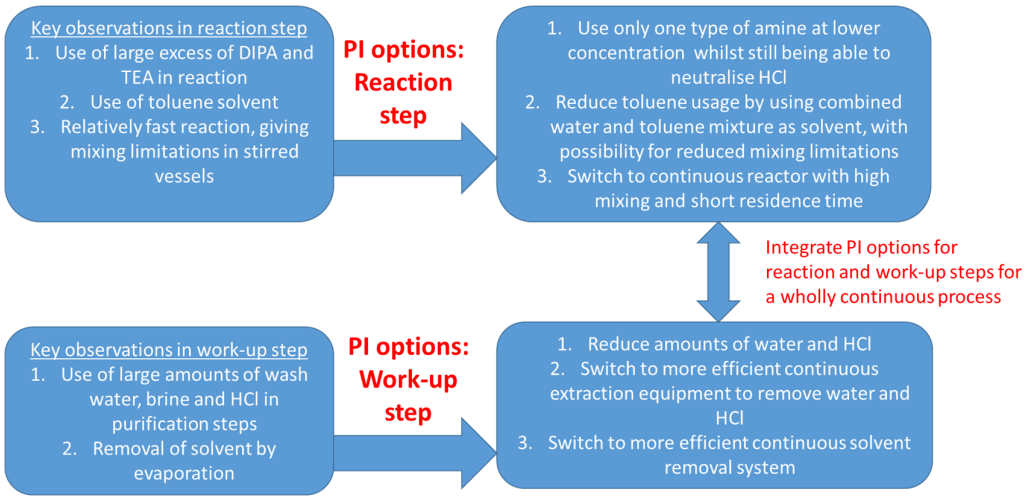


Figure 5. PI options in reaction and work-up steps of amidation process

The feasibility of the PI options are discussed in detail below.

3.2.1 Reduce Number and Amount of Reagents Used

The premixing of DIPA and TEA step prior to the reaction could be avoided by replacing TEA with DIPA, given that DIPA has similar basicity as TEA. The reduction of

DIPA from 3 to 2.1 mol eqv (with respect to moles of CBC) did not affect the efficiency of capturing HCl. The conductivity test on the aqueous phase which showed that 97% of the HCl was converted to DIPA.HCl, which indicated a highly efficient capture of HCl. Table 1 shows the potential cost saving if Option 3 was selected.

Table 1. Cost comparison of amine reagents

	Options	**Cost (USD/kg amide 1)**
1)	3 mol eqv DIPA	122
2)	1.5 mol eqv TEA+ 1.5 mol eqv DIPA	112
3)	2.1 mol eqv DIPA	86

3.2.2 Reduce Toluene Usage

Whilst it is recognized that there may be opportunities to replace the toluene solvent (b.p. 110°C) with other more benign alternatives such as anisole[13] (b.p. 155°C) and p-xylene[14] (b.p. 138°C), these solvents have higher boiling points and are often more expensive than toluene. With solvent recycling in mind, toluene with the lowest boiling point is selected in the present study for greater energy efficiency during recycling by evaporation.

To eliminate mixing limitation caused by amine salt (solids), a small amount of water could be added to the solvent (toluene) as the amine salt is highly soluble in water (500 g/L). Based on visual observation during the reaction, there was no formation of solid and the reaction mixture appeared cloudy as the organic and aqueous phases were dispersed under the agitation of a single impeller at 450 rpm. The result indicated that close to 100% product yield was reached in less than 5 min as shown in Figure 6A, proving that the use of toluene-water mixture as solvent can effectively avoid mixing limitation compared to a single organic solvent phase at the same concentration of the limiting reagent CBC (Figure 6B).

By elimination of mixing limitation due to solids, a higher initial CBC concentration in toluene was explored. The initial CBC and DIPA concentrations in toluene were doubled to 1 M and 2.1 M respectively. Under these conditions, 100% product yield was achieved in less than 90 s (Figure 6A), as the rate of reaction increases at higher concentrations. Even though the toluene-water system might be capable of operating at even higher reagent concentrations, the decision was made to cap the initial CBC and DIPA concentrations at 1 M and 2.1 M, as CBC has limited solubility in toluene and it might take a longer time for complete dissolution of the CBC in toluene if higher concentrations were used.

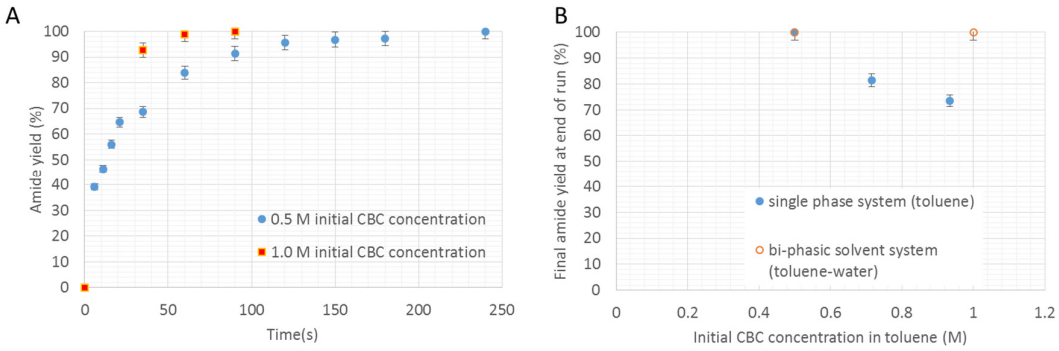


Figure 6. Effect of solvent system on amide yield in batch A) reaction profile in bi-phasic (toluene-water system) at different initial CBC concentration in toluene B) bi-phasic vs single organic phase solvent on final amide yield (all yield measurements have a standard error of ±3%)

3.2.3 Reduce Wash Medium in Separation Process

The amounts of wash solvents used in the safe and scalable batch process were investigated (Table 2). In workup step 1, the amount of water to fully dissolve the salts could be reduced by 55% relative to the reported value (0.63 L/mol CBC) by Faigl, et al. [6]. In workup step 2, the amount of HCl wash required for neutralization of excess DIPA was reduced

significantly, given that the required mole equivalent of DIPA was decreased from 3 to 2.1 (section 3.3.1).

Table 2. Summary of the improvement actions taken to minimise amount of wash medium used (deviations in concentrations and amide yield based on measurement error and repeat measurements of 3 replicates respectively)

Workup step	Reagents	Literature data [6]	PI option	Crude sustainability benefits	Amide 1 yield in organic phase (%)
1) Water wash and phase separation	Water	0.63 L/mol CBC	**0.28 ± 0.02 L/mol CBC (minimum)**	55%±3% reduction in volume of water usage	98±3
2) HCl wash and phase separation	5 w/w% (1.44M) HCl	0.47 L/mol CBC	**0.07 ± 0.02 L/mol CBC**	85%±4% reduction in volume of HCl solution usage	96±3
3) NaCl wash and phase separation	1 M NaCl solution	0.47 L/mol CBC	0.47 ± 0.02 L/mol CBC is the minimum amount required to remove the remaining salt in toluene	-	94±3

While amide 1 yield residing in the organic phase decreased after each aqueous wash (Table 2), no trace of amide 1 was observed in the respective discarded aqueous phases after phase separations. This suggested that the loss of amide 1 was more likely due to handling which could be designed to be minimized during scale-up.

3.2.4 Continuous reaction

The use of toluene-water solvent system in the intensified case was able to avoid the formation of solid amine salt, which made it compatible with continuous mode of reaction. The reaction was mixing sensitive and required a relatively short time (within 5 min) to achieve full

conversion. Given that CBC could decompose in the presence of water, the residence time should be minimised in order to limit the exposure of CBC to water.

Such conditions were suitable for conventional intensive flow reactor such as static mixer which offers good mixing and short residence time. As such, the proof of concept was experimented with static mixers under a range of conditions as highlighted in Figures 7A-C. Yield increases with residence time at constant flow rate and Re as shown in Figure 7A where higher residence time at a fixed flowrate is achieved in a longer length of plain tube attached to the end of the static mixer section. However, slugs of liquid-liquid segments were observed in the 1/8" PTFE bare tube, suggesting that poor mixing between the streams may be slowing the reaction down in the longer lengths of plain tube after the static mixer section i.e the reaction becomes mixing limited at the high residence times. The effect of increasing flowrate (and consequently Re) in Figure 7B further highlights the importance of good mixing in achieving high product yields especially in longer lengths of plain tube, corresponding to the higher residence times of 70 s. Reaction may also be speeded up by increasing the reagent concentration as indicated in Figure 7C whereby 100% yield is attained at 195 s residence time once steady state has been achieved after about 10 minutes of run time.

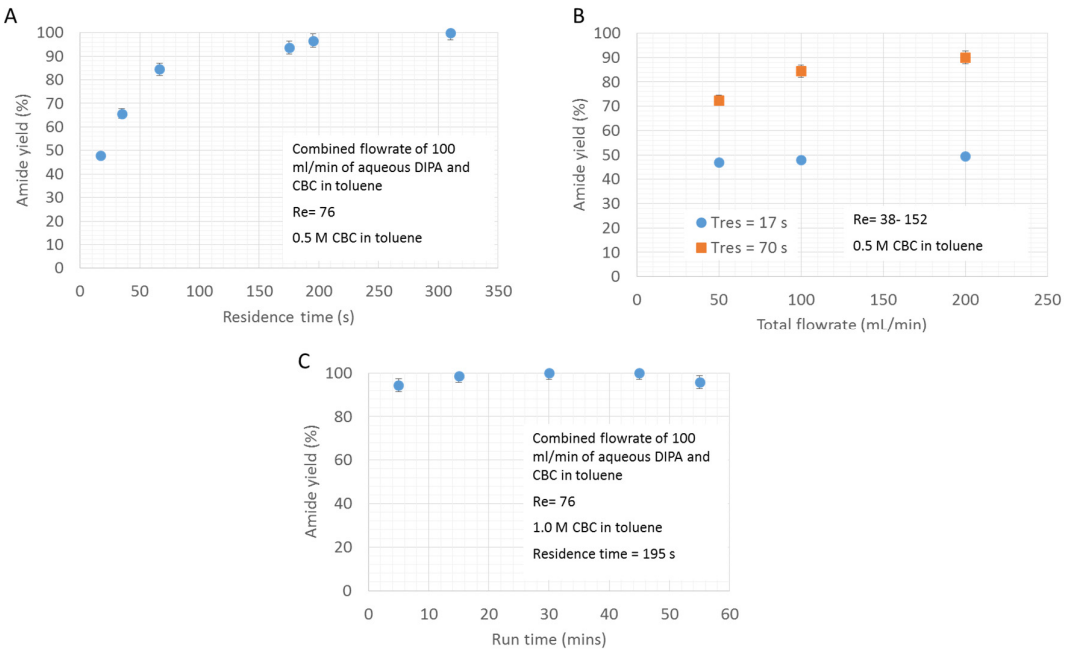


Figure 7. Static mixer tests for the reaction step in continuous mode A) effect of residence time in static mixer on product yield B) Effect of flowrate and mixing on product yield at two different residence times higher residence times are obtained with longer length of plain PTFE tube C) Higher concentration effect on product yield (all yield measurements have a standard error of ±3%)

As seen in Figure 7C, complete conversion was feasible under the applied reaction condition (100 ml/min combined flowrate at the higher CBC concentration). Based on this promising result, the static mixer reactor setup was considered as a feasible example for continuous amidation. Further work could be done to explore the application of other continuous reactors with good mixing and short residence time.[15-17]

3.2.5 Continuous whole process

In view of a continuous flow reaction, a continuous operation incorporating continuous workup was investigated. A potential continuous process involved a static mixer reactor and

subsequent continuous separation equipment such as centrifugal extraction, Karr column, agitated thin film dryer, spray dryer and wiped film evaporator. There are many other possible continuous workup equipment that might be applicable. For the ease of determining the actual feasibility of the technology, experiments were performed with equipment that were available in-house such as the centrifugal extractor (CE) and the wiped film evaporator (WFE).

The CE was used in three liquid-liquid phase separation steps - 1) separation of aqueous and organic phase; 2) extraction of excess DIPA from the organic phase using 1 M HCl solution; and 3) removal of any remaining salts in the organic phase using 1 M NaCl solution. For all the phase separations, clear organic and aqueous streams were collected from the outlets. For the second liquid-liquid separation, almost complete removal of DIPA from organic phase was achieved for the given operating condition according to NMR analysis of the organic phase. For the third liquid-liquid separation, due to lack of analytical method to quantify amine salt in the organic phase, it was conservatively assumed that the CE would be equally efficient in amine salt extraction as stirred tank reactor. In general, the extraction using CE is considered superior to batch as the mixing and phase separation can be completed in seconds compared to minutes in stirred tank reactor.

The use of WFE was aimed at obtaining amide 1 as free-flowing dry solid by removing toluene continuously through a heated column under reduced pressure. In the first trial, despite operating at the highest temperature and lowest pressure possible, only 24 v/v% of toluene was removed, under a flow rate of 60mL/min. The short residence time of the reaction mixture in the heated column was identified as the limitation to further evaporation. In order to extend the residence time in the fixed length column, the lowest possible flow rate of 43 mL/min was used. The result improved with removal of 33 v/v% of toluene. A second pass was made under

the same condition and a further 22 v/v% was removed. At this point, the existing WFE had removed more than half of the solvent in two passes. Although multiple passes were required to obtain the desired product specification, the available WFE has shown promising and optimistic results. It can be envisaged that an appropriately designed WFE providing a large enough surface area for evaporation for this specific application could successfully remove a large amount of solvent (>90% v/v) in a single pass or in multiple passes.

The experimental studies with the CE and WFE in this present work, although limited in scope, serve to highlight the feasibility of using these intensified technologies in the purification of the amidation end-product and their general application in pharmaceutical processing. Further experimental investigations are warranted if higher separation and recovery efficiencies are to be demonstrated in practice.

3.3 Safe and Scalable Batch Case

The base case is defined as a conventional manufacturing process, which is in batch mode, where the reaction occurs, followed by workup, often in the same reactor vessel. In order to make a fair comparison between the base case and the intensified options, the base case was reviewed to ensure that it would be operable at scale.

It was observed that, according to the lab-scale procedure,[6] white HCl fume was released during the reaction where the mixture of DIPA and TEA bases was added to the solution of CBC in toluene. To improve the operability of the reaction at scale, the quenching of HCl was made more efficient by changing the addition sequence – CBC was added slowly to a solution of bases in toluene instead. With this modification, noticeably lesser HCl fume was released during the reaction because CBC was added to a large excess of bases where the concentration of amine bases is significantly higher than CBC and HCl. As a result, HCl was quickly ‘taken’ by the bases that are present in abundance.

Another issue encountered at lab-scale was the formation of hard and clumpy solid after the evaporation of crude reaction mixture, which was found to be caused by the presence of minute amounts of water present during solvent evaporation. This problem could be solved by drying the reaction mixture using anhydrous magnesium sulfate prior to solvent evaporation. Thereafter, easy-to-flow crystalline solid product could be obtained.

3.4 Development of batch base case and intensified cases for the whole process

Following the feasibility assessment of the identified PI options, optimum operating conditions for which are summarised in Table 4, an appropriate decision-making step focusing on the whole process (from starting material to product) is required. This decision would consider, for instance, whether it is more worthwhile to retain a batch process, or to convert either entirely to a continuous process or partially to flow (e.g. continuous reaction –batch workup hybrid mode). As pointed out by Teoh, et al. [10], this decision could be made based on qualitative benefits in terms of crude cost of the identified PI options. In order to estimate the process operating expenditure, the process flow schemes for the different cases are developed and additional work such as simulation was required to support the design wherever experimental data was unavailable. For example, the continuous vacuum filtration unit was conceptually designed (e.g. equipment sizing, energy and process efficiency) based on practical assumptions. However, it is clear that the practicality of the processes designed has to be validated in future work.

One key difference to highlight is the water consumption between the intensified batch case and continuous cases, as shown in Table 3. For the continuous cases, pre-mixing of DIPA in water (solubility of DIPA in water~100g/L) was required to fully dissolve DIPA in water to obtain a homogeneous aqueous stream of DIPA. This is a critical step as the amount of DIPA

added into the reaction system was directly controlled by the flow rate of the aqueous DIPA solution. Without complete dissolution, DIPA and water would separate out into two phases, where it would be challenging to control the flow rate of DIPA.

On the other hand, in the intensified batch case, DIPA was not required to be fully dissolved in water as the batch case allowed addition of multiple streams. The DIPA stream was added directly into the batch reactor vessel, separate from the addition of toluene, water and CBC streams. As a result, the water usage in continuous cases was estimated to be seven times higher than that in the intensified batch case.

Table 3. Summary of the operating conditions in the batch base case and intensified batch case, continuous reaction and continuous whole process

	Literature case (not scalable)	**Batch base case (scalable)**	**Intensified batch case**	**Continuous reaction**	**Continuous whole process**
Mode of reaction	Batch			Continuous	Continuous
Mode of separation	Batch				Continuous
Solvent system	Toluene	Toluene	Toluene-water		
Recycling of solvent	No	No	Yes		
Required residence time	24 h	3 min (Theoretical)	90 s	5 min	
Sequence of addition	Mixture of TEA & DIPA added to a mixture of CBC in toluene	CBC added to a mixture of TEA & DIPA in toluene	CBC added to DIPA in toluene-water mixture	CBC in toluene mixed with DIPA in water	
Concentration of limiting reagent (CBC)	0.5 M	0.5 M	1 M (in toluene)		
Reagents	TEA – 1.5 mol. eq.	TEA – 1.5 mol. eq.	DIPA – 2.1 mol. eq.		
	DIPA – 1.5 mol. eq.	DIPA – 1.5 mol. eq.			
Reaction yield	>99%				

Work up	Water wash	Water wash	HCl wash		HCl wash in CE
	HCl wash	HCl wash	1 M NaCl solution wash		1 M NaCl wash in CE
	Brine wash	1M NaCl solution wash	Anhydrous $MgSO_4$ addition		Anhydrous $MgSO_4$ addition in CSTR
	$MgSO_4$ drying	Anhydrous $MgSO_4$ addition	Filtration		Continuous filtration
	Filtration	Filtration	Evaporation of toluene		Wiped film dryer
	Distillation	Evaporation of toluene	Drying		-
	Trituration with Hexanes	Drying	-	-	-
	Filtration	-	-	-	-
	Drying	-	-	-	-
Recycling of solvent	No	No	Yes		
Water consumption	0.7 L/mol CBC	0.7 L/mol CBC	0.3 L/mol CBC	2.1 L/mol CBC	

3.5 Design of batch base case, intensified batch case, continuous reaction case and continuous whole process case for 3.3 tonnes per year Amide 1 production

In order to compare the sustainability benefits between the batch base case, intensified batch case, continuous reaction case and continuous whole process case, the plants were designed to produce about 3.3 tons per year of amide 1 from CBC and DIPA, with amide yield of 100% after reaction (based on CBC), downstream amide purity of about 99 w/w% and less than 0.1 w/w% of residual toluene. The throughput was selected based on the reaction conditions and results obtained from the continuous static mixer flow reactor, assuming the operation hours per year to be 8000 h. The recycling of evaporated toluene for subsequent batches is conceptually incorporated in the design of the intensified batch and continuous cases. The process flowsheet for each of the four processes are shown in Figures 8-10.

The following assumptions were made based on lab-scale experimental work:

1) There was no side product observed from the reaction based on ^{1}H NMR spectra.
2) There was no observable degradation of CBC when in contact with water based on the amide 1 yield obtained.
3) No observable heat of neutralisation was detected when excess DIPA and HCl solution are mixed together.
4) During the HCl wash step, all the excess DIPA was assumed to be reacted and removed in the aqueous phase as observed from ^{1}H NMR spectra.
5) During the NaCl solution wash step, all the amine salt was assumed to be removed in the aqueous phase.
6) All amide 1 losses were assumed to be due to handling as no organics is observed in the aqueous phase based on GC analysis.
7) 90% of the toluene used in intensified batch case, continuous reaction and continuous process was assumed to be recycled.
8) The reactors were assumed to have good containment so there was no loss of volatile amines to the atmosphere.
9) Total number of operation hours per year was assumed to be 8000 h for the continuous processes while batch cycles times were estimated to be 13 hours including work-up stages.

Lab scale experimental heat and mass balances were applied to determine the production scale size of the batch reactor, resulting in a batch reactor of approximately 127 L volume producing 5.4 kg of amide product per batch in an assumed 13 hour batch cycle including work-up for the batch base case, whilst the intensified batch vessel employing the bi-phasic solvent system and higher reagent concentrations was significantly smaller in volume (25 L) and

produced about 7 kg amide per batch. A similar procedure was applied to the continuous reaction process based on a static mixers (0.5 L volume) operated continuously over 8000 hours per year, with a CSTR in the sequential step downstream of the static mixer for the continuous wash steps in the process (as shown in Figure 9).

In the batch base case, intensified batch case and continuous reaction case, besides experimental results being applied to a conceptual scaled up filtration step, simulation was performed using DynoChem software[18] to develop the operation time for the solvent evaporation and drying steps and their heat and mass balances based on specifications of commercially available equipment. The feed conditions used in the simulations for the work-up steps were based on experimental outlet conditions from upstream units. The methodology employed for these sequential batch downstream processing simulations is highlighted in the Supporting Information 2.

The continuous whole process case (Figure 10) consisted of continuous reaction and separation. The continuous extractions are designed to be performed using three CE in series, under similar operating conditions as the laboratory tests over a continuous duration of 8000 hours/annum. Although the WFE employed in the laboratory tests demonstrated its feasibility to remove solvent continuously, its performance was far from ideal at 55% toluene removal after two stages. For the purpose of the design, it is assumed that a state-of-the-art agitated thin film dryer which operated based on the same principle as the WFE would be able to meet the expectation in a single pass. An ideal WFE performance at 90% toluene removal was therefore simulated in DynoChem[18] on the basis of a larger surface area (0.25 m^2) than the lab scale unit (0.108 m^2) being achieved; the methodology and optimization steps for this are highlighted in the Supporting Information 2. Other conceptually developed continuous operations included the continuous feed of anhydrous magnesium sulfate using an automatic screw feeder, a well-mixed CSTR to suspend the magnesium sulfate and a continuous filtration of the slurry, all of

which were based on extrapolation of lab scale data, as highlighted in the Supporting Information 2.

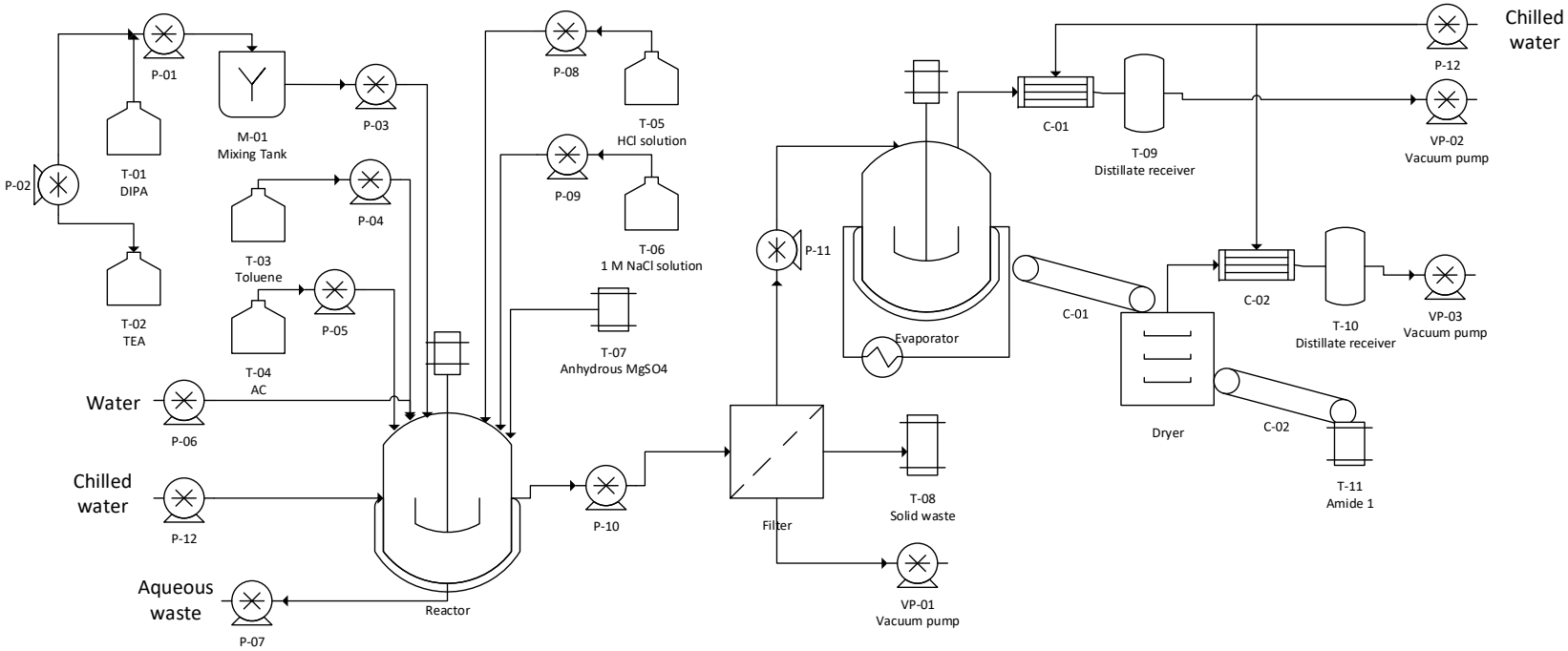


Figure 8. Schematic process diagram for large scale batch base case and intensified batch processes

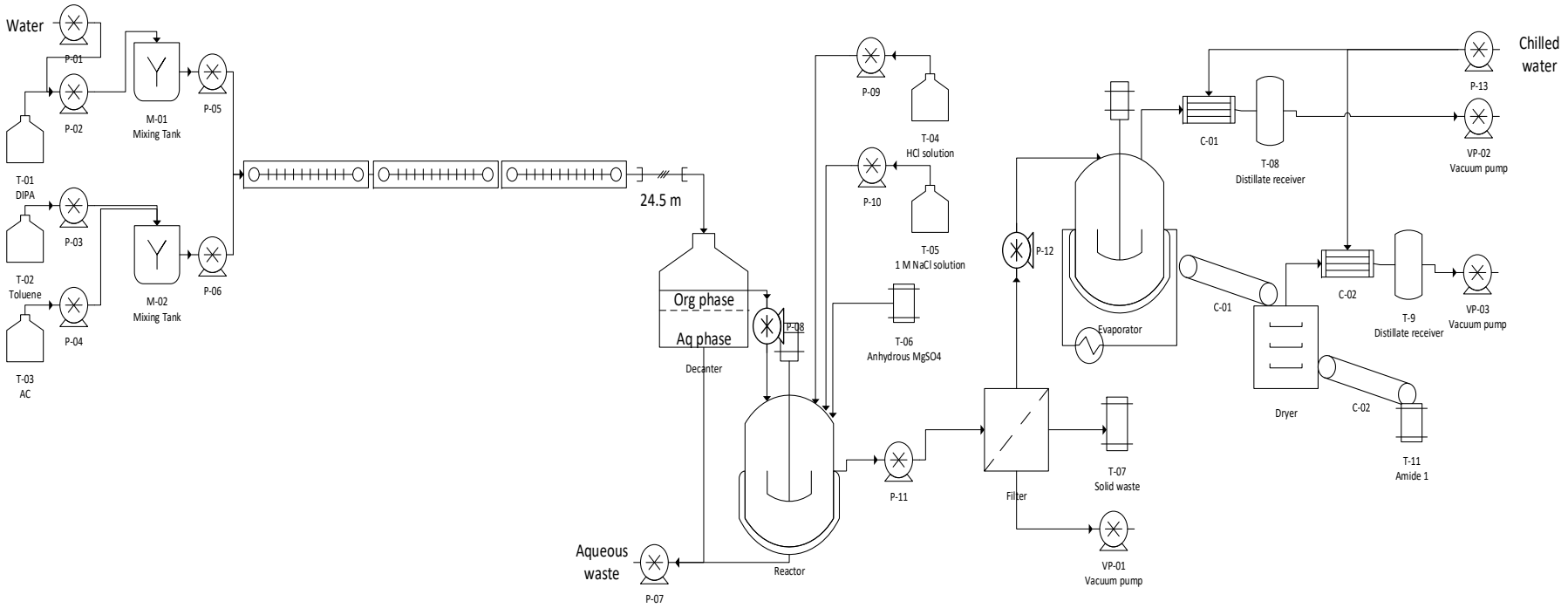


Figure 9. Schematic process diagram for continuous reaction case using static mixers in reaction stage

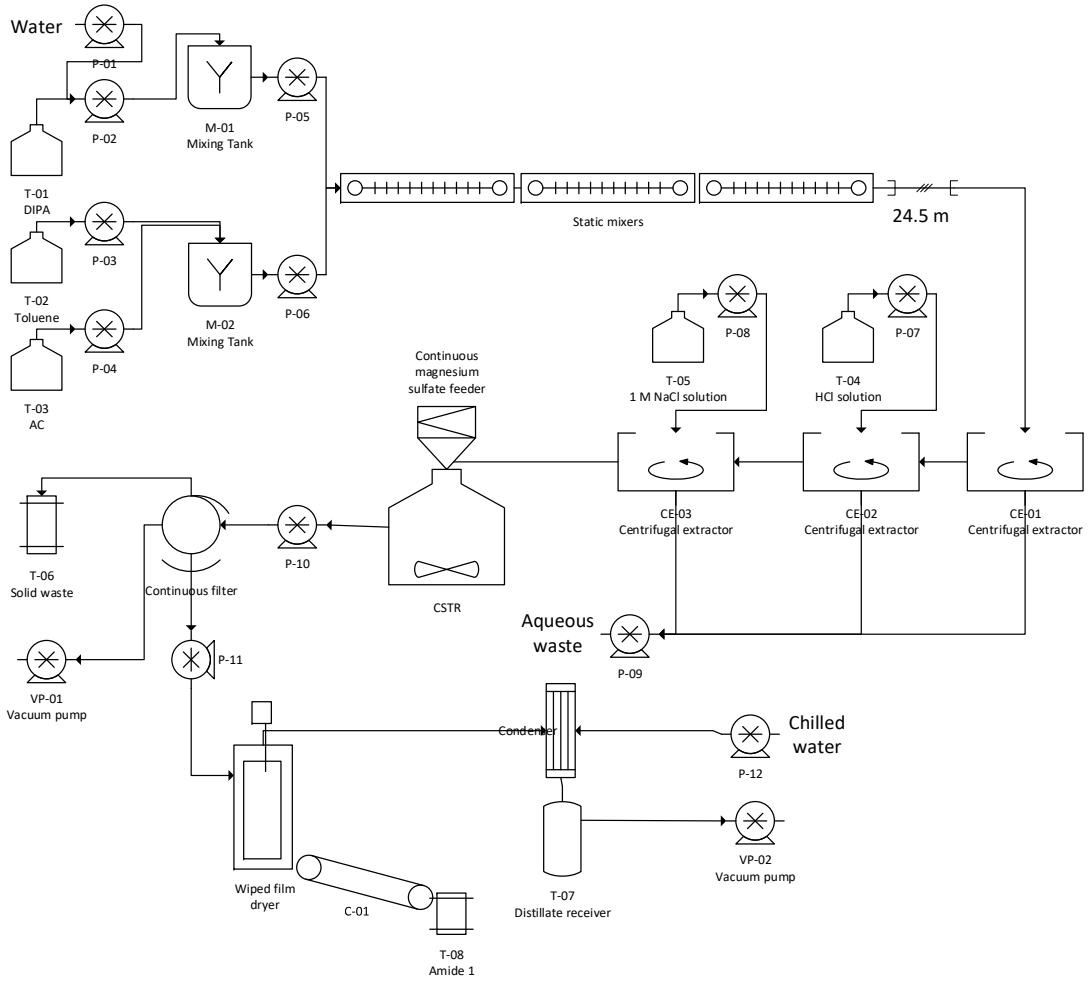


Figure 10. Schematic process diagram for wholly continuous process

3.6 Comparisons of sustainability performance

Based on the process design for the four cases, their sustainability performances in terms of economy, mass, energy and environmental efficiencies are summarized in Table 4 following the approach employed in our earlier studies.[10, 19] In terms of the material efficiency and E-factor, the intensified batch case is the best performer. The poorer performance of the continuous cases is due to significant amount of water used to dissolve DIPA in order to introduce DIPA as an aqueous stream to the organic stream containing CBC. This is unnecessary in the intensified batch case where toluene, DIPA, water and CBC are added separately into the batch reactor and significantly lesser amount of water is required as the amine salt is highly soluble in water.

Based on Table 4, the continuous cases (835 kg amide 1/h/m^3) have significantly higher reaction volume efficiency than the batch cases (17 kg amide 1/h/m^3) because the static mixer reactor volume is much smaller than the batch reactor vessels and the batch cases have relatively longer cycle time (one-pot reaction) which require larger reactor volumes in order to cope with the required throughput.

The two most energy intensive cases are the batch base case and the continuous whole process case. The majority of the energy in the batch base case is consumed by toluene evaporation, as its initial CBC concentration was more dilute than in other cases. For the continuous whole process case, most of the continuous equipment, including the centrifugal extractors, the screw feeder and the agitated thin film dryer, required mechanical movement/agitation that is energy intensive.

To assess the robustness of the design for the different configurations, a sensitivity analysis based on a 10% decrease in the amide yield has been performed, the results for which are also indicated in Table 4. It is observed that most of the parameters of interest are increased by a similar margin of the order of 10-12%, apart for the E-factor for the intensified batch case

which is increased by 15%. This is due to the same quantity of increased organic waste of unreacted material (CBC and DIPA) being added to a smaller amount of existing waste compared to the other cases. The 10% margin on energy efficiency and OPEX is nevertheless sufficient for the continuous reaction system to become an attractive option with respect to the intensified batch case, assuming that the continuous reactor and the associated downstream processing can maintain a consistent amide yield of 100%. This is feasible as small, continuous reactors tend to be associated with less variability at chosen operating conditions than larger batch reactors, provided robust downstream separations can be implemented.

Table 4. Comparisons of sustainability metrics between batch base case, intensified case, continuous reaction, and continuous process at design scale of about 3.3 tonnes amide 1 per year (values in brackets denote the results of a sensitivity analysis on the selected design outputs based on a reduction of amide yield from 100% in the optimal case to 90% whilst keeping the production capacity constant)

	Batch base Case	Intensified batch case	Continuous reaction	Continuous whole process
Total material efficiency (kg material /kg amide 1)	21(↑11%)	**6**(↑11%)	15(↑10%)	15(↑10%)
E-factor (kg waste/kg amide 1)	20 (↑12%)	**5**(↑15%)	14(↑12%)	13(↑12%)
Reaction volume efficiency (kg amide 1 /h/m^3)	3	17	**835**	**835**
Reaction and separation volume efficiency (kg amide 1 /h/m^3)	0.001	0.007	0.013	**5.644**
Total energy efficiency (kJ/kg amide 1)	454,784 (↑11%)	**149,927** (↑10%)	167,069 (↑10%)	420,338 (↑11%)
OPEX (USD/kg amide 1)	369 (↑11%)	**220** (↑10%)	**227** (↑10%)	253 (↑10%)
Economic savings in OPEX (%)	Benchmark	**40**	**39**	32

The operational expenditure (OPEX) derived in this study included the cost of raw materials, utilities/energy and waste treatment as shown in Figure 11. They are priced based on the same source of costing database. Given that the water consumption in the continuous cases is much higher than the intensified batch case, the amount of aqueous waste incurred in the former is much greater than the latter. While cost of water is relatively cheap, the cost of aqueous waste treatment costs could be considerable. As such, the intensified batch base case achieved the lowest OPEX of 220 USD/kg amide 1, due to lower solvents usage and therefore, cost savings in waste treatment cost.

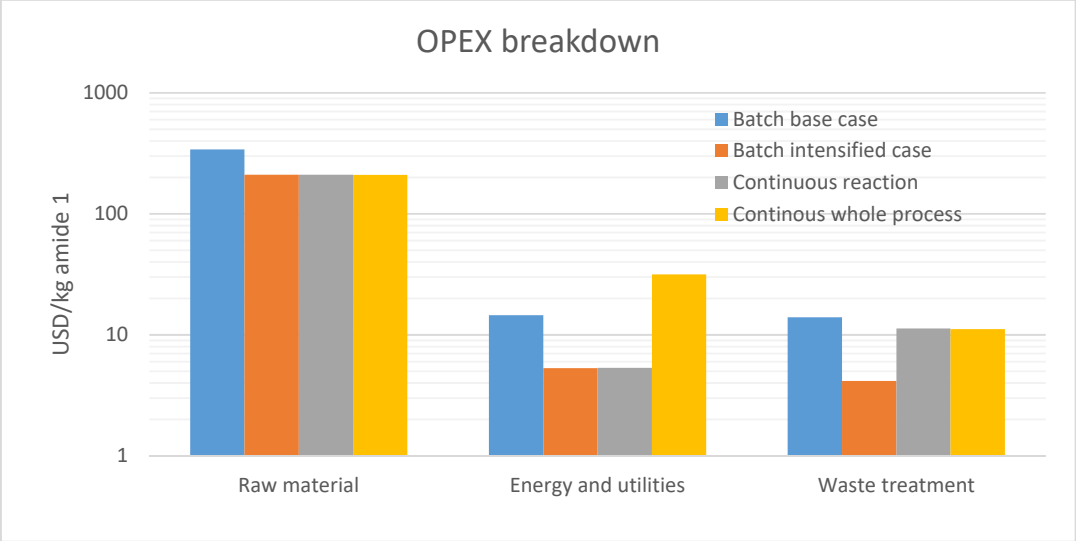


Figure 11. Breakdown of OPEX for all 4 cases.

4. Conclusion

The result of this study indicates that the largest overall cost reduction potential is the intensified batch case as the waste and energy costs are relatively low compared to the continuous reaction and continuous process cases. It uses the least amount of reagents and solvents among all the cases leading to least material processed and least energy demanded overall, which is significant from an environmental point of view. The impacts of several process improvement actions using the batch process make this the greenest process. However,

a sensitivity analysis demonstrates that a reduction in amide yield to 90% in the intensified batch could result in the continuous reaction scheme operating at 100% amide yield becoming a more attractive option on the basis of OPEX and energy efficiency.

In this study, the sustainability analysis showed that continuous whole process did not bring the most benefits. It is recognized that the continuous cases resulted in higher water consumption and solvent waste generation due to low DIPA water solubility. Although this did not negatively affect OPEX to a great extent as cost of water is relatively cheap, the effect on E-factor and material efficiency is significant.

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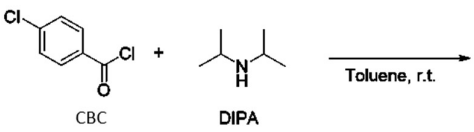
Supporting information

Supporting Information 1: Table S1. Lab-scale batch amidation reaction and work-up characteristics and the corresponding PI options is included in the Supporting Information file.

Supporting Information 2: Scale-up methodologies and simulations models

This information is available free of charge via the Internet at http://pubs.acs.org/

TOC



CBC DIPA Amide 1

Major process bottlenecks identified:
X Mixing limitation caused by formation of 'sticky' solids
X Large amount of DIPA and TEA excesses used

Sustainability metric	Batch base case	Intensified Base Case	Continuous reaction	Continuous whole process
Mode of reaction	Batch		Continuous	Continuous
Mode of separation	Batch			Continuous
Solvent system	Toluene		Toluene-water	
Total material efficiency (kg material/kg amide 1)	21	6	15	15
E-factor (kg waste/kg amide 1)	20	5	14	13
Economic savings in OPEX (%)	Benchmark	40	39	32